Original Article

Low tidal volume ventilation strategy and organ functions in patients with pre-existing systemic inflammatory response

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Abstract

Background and Aims: Ventilation can induce increase in inflammatory mediators that may contribute to systemic organ dysfunction. Ventilation-induced organ dysfunction is likely to be accentuated if there is a pre-existing systemic inflammatory response.

Material and Methods: Adult patients suffering from intestinal perforation peritonitis-induced systemic inflammatory response syndrome and scheduled for emergency laparotomy were randomized to receive intraoperative ventilation with 10 ml.kg^{-1} tidal volume (Group H) versus lower tidal volume of 6 ml.kg^{-1} along with positive end-expiratory pressure (PEEP) of 10 cmH_2O (Group L), (n = 45 each). The primary outcome was postoperative organ dysfunction evaluated using the aggregate Sepsis-related Organ Failure Assessment (SOFA) score. The secondary outcomes were, inflammatory mediators viz. interleukin-6, tumor necrosis factor-α, procalcitonin, and C-reactive protein, assessed prior to (basal) and 1 h after initiation of mechanical ventilation, and 18 h postoperatively.

Results: The aggregate SOFA score (3[1–3] vs. 1[1–3]); and that on the first postoperative day (2[1–3] vs. 1[0–3]) were higher for group L as compared to group H ($P < 0.05$). All inflammatory mediators were statistically similar between both groups at all time intervals ($P > 0.05$).

Conclusions: Mechanical ventilation with low tidal volume of 6 ml/kg^{-1} along with PEEP of 10 cmH_2O is associated with significantly worse postoperative organ functions as compared to high tidal volume of 10 ml.kg^{-1} in patients of perforation peritonitis-induced systemic inflammation undergoing emergency laparotomy.

Keywords: Biotrauma, low tidal volume, protective lung ventilation, sepsis

Introduction

Biotrauma refers to ventilation induced increase in inflammatory mediators within lungs that may leak into circulation consequent to damage of alveolo-capillary membrane and thus result in a systemic inflammatory response.[1] Occurrence of biotrauma has been documented by increase in various inflammatory mediators such as interleukin (IL)-6, IL-1β, IL-8, tumor necrosis factor-alpha (TNF-α), and several coagulation factors following both long[2] as well as short-term mechanical ventilation.[3-5] Decrease in biotrauma occurs with use of a lung protective ventilation strategy employing low tidal volumes.[2-9]

It is hypothesized that biotrauma leads to injury of the systemic organs thus contributing to their dysfunction or failure.[10,11] Propensity of biotrauma to cause organ dysfunction is likely to be accentuated if there is a pre-existing systemic inflammatory response e.g., due to sepsis. Patients with perforation peritonitis

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present with systemic inflammatory response following the intra-abdominal sepsis and majority of deaths are known to occur due to its progression to organ dysfunction/failure.[12]

Against this background, we aimed to evaluate the role of intraoperative ventilation using high tidal volume versus a lung protective strategy using low tidal volume, in causing or worsening postoperative organ dysfunction in patients with pre-existing systemic inflammation due to perforation peritonitis. The effect on systemic inflammatory mediators including the cytokines IL-6 and TNF-α; and acute phase reactants viz., procalcitonin and C-reactive protein (CRP) was evaluated as a secondary objective.

The null hypothesis was that there is no difference in the postoperative organ dysfunction evaluated using the aggregate Sepsis-related Organ Failure Assessment (SOFA) score, in patients of perforation peritonitis undergoing emergency laparotomy following intraoperative ventilation with low tidal volume of 6 $ml.kg^{-1}$ along with positive end-expiratory pressure (PEEP) of 10 cmH_2O, or a high tidal volume of 10 $ml.kg^{-1}$ without PEEP.

Material and Methods

This randomized controlled double-blinded trial was undertaken after approval of the Institutional Ethical Committee-Human Research (dated; on 1.5.2010) and obtaining written informed consent from all the subjects. Its duration was from October 2010 to July 2015.

Ninety adult patients aged between 18 to 65 years, suffering from intestinal perforation peritonitis-induced systemic inflammatory response syndrome, and scheduled for emergency laparotomy under general anesthesia were included. Those who were anticipated to require mechanical ventilation in postoperative period, with a history of any organ dysfunction or immunosuppression unrelated to the presenting illness, or recent ICU admission for mechanical ventilation (<1 year) were excluded from the trial. Those on inotropic support, or suffering from traumatic or iatrogenic perforation peritonitis were also excluded.

Patients were randomized into two groups by using a computer-generated random number table in blocks of 5 according to the strategy of intraoperative mechanical ventilation ($n = 45$ each). Patients in group H were ventilated intraoperatively using the higher tidal volume of 10 $ml.kg^{-1}$ while those in group L ($n = 45$) received a lower tidal volume of 6 $ml.kg^{-1}$ ideal body weight along with PEEP of 10 cmH_2O.

In both the groups, mechanical ventilation was instituted with a tidal volume and PEEP as per group allocated. The respiratory rate was initiated at 10 breaths/min and further titrated to maintain eucapnia ($ETCO_2$ = 35–40 mmHg), while the ratio of inspiratory to expiratory time was kept constant (1:2) throughout.

Except for the difference in intraoperative ventilation strategy, perioperative management was similar in both groups.

In the pre-operative room, an intravenous catheter was inserted through antecubital vein (peripherally inserted central catheter). Patient was shifted to the operating room and lead II electrocardiography, pulse oximetry, capnography, non-invasive oscillometric blood pressure, and central venous pressure monitoring were instituted using an S-5 monitor (Datex-Ohmeda®, Madison, Wisconsin, USA). Ringer's lactate was infused to attain a central venous pressure of at least 8 mmHg.

After preoxygenation and fentanyl 2 $\mu g.kg^{-1}$ IV, anesthesia was induced with propofol 1–2.5 $mg.kg^{-1}$ IV and intubation facilitated by rocuronium 0.9 $mg.kg^{-1}$ IV. Anesthesia was maintained with oxygen and nitrous oxide along with isoflurane. FiO_2 was titrated to maintain SpO_2 ≥95%. Analgesia was supplemented with fentanyl in 10 μg aliquots; and muscle relaxation with rocuronium 0.1 $mg.kg^{-1}$ IV boluses. At end of surgery residual muscle blockade was reversed with glycopyrrolate (0.01 $mg.kg^{-1}$ IV) and neostigmine (0.05 $mg.kg^{-1}$ IV).

Intraoperatively Ringer's lactate infusion was initiated at 10 $ml.kg^{-1}.h^{-1}$ with further volumes decided by the attending anesthesiologist according to the central venous pressure and hemodynamic variables. Dopamine infusion was initiated if mean arterial pressure decreased to <60 mmHg despite adequate fluid resuscitation. Blood was transfused to maintain a hematocrit of at least 30%.

The perioperative management including postoperative analgesia was similar and as per routine clinical practice in both groups. Postoperative analgesia protocol in our institution involves multimodal intravenous analgesia using opioids in anesthesia recovery room, followed by paracetamol 1 g IV qid, and tramadol 2 $mg.kg^{-1}$ IV as required to maintain the Visual Analog Scale (VAS) score <4, and diclofenac was used as a rescue.

Postoperatively the SOFA score was calculated daily till patient's discharge or death, by considering the worst value for each organ system in a 24-h period. From the daily SOFA scores, aggregate and maximum SOFA scores were

calculated at the end of hospital stay. Aggregate SOFA was calculated by summing the worst score for each organ system over the entire duration.[13] Maximum SOFA was the highest total SOFA score attained over the entire duration of hospitalization.[13]

The anesthesiologist recording postoperative outcome measures including SOFA score was not aware of the patient's group allocation.

To assess the magnitude of systemic inflammatory response to mechanical ventilation strategy, blood samples were assessed for IL-6 and TNF-α in all patients; and procalcitonin and CRP in 7 and 11 patients of group H and L, respectively. Sampling was done just prior to mechanical ventilation after induction of anesthesia (baseline value), 1 h after mechanical ventilation, and 18 h postoperatively. The sample of 5 ml of blood was collected aseptically and allowed to stand at room temperature for 1 h to clot. The serum was removed and placed in new tube. Serum was stored at −80°C till further use. For the inflammatory mediators' assay, serum was seeded on a 96 well plate, supernatants harvested and the markers were measured by commercially available enzyme-linked immunosorbent assay according to manufacturer's instruction. The detection limit for IL-6 (Diaclone,® France), TNF-α (Diaclone,® France), procalcitonin (Biovendor,® Czech Republic), and CRP (DRG,® Germany) was 2 $pg.ml^{-1}$, 8 $pg.ml^{-1}$, 10 $ng.ml^{-1}$, and 15 $pg.ml^{-1}$, respectively.

Site of perforation, duration of surgery and mechanical ventilation, intraoperative use of dopamine, and highest FiO_2 were noted. The in-hospital mortality and incidence of re-exploration due to any surgical reason were also noted. Postoperative data were censored at the time of re-exploration.

For comparison of preoperative severity of illness SOFA[14] and APACHE II scores were noted.[15] The Mannheim Peritonitis Index (MPI) score[16] was calculated for assessment of severity of peritonitis.

Ancillary clinical observations included various intraoperative ventilatory parameters. The values for these parameters obtained after initiation of mechanical ventilation were taken as baseline for comparison.

At a power of 80% and α-error of 5%, 42 patients were required in each group to detect 25% decrease in aggregate SOFA score.[17] To accommodate possible dropouts due to any reason including unanticipated postoperative mechanical ventilation, 45 patients were enrolled in each group.

Statistical analysis was done using the software SPSS (version 23). For intergroup comparisons, qualitative data were analyzed using the Chi-square test or Fisher's exact test; and quantitative data using unpaired *t*-test or general linear model of analysis of variance (ANOVA) for those repeated intraoperatively. Values for inflammatory mediators were log transformed before applying ANOVA. Daily SOFA scores were not normal in distribution and hence compared using the Mann–Whitney test. A P value <0.05 was considered significant. For statistical analysis of the repeated intraoperative ventilatory measures readings were truncated at 75 min since beyond this time there was significant attrition of data due to completion of surgery.

Results

The demographic parameters, and the preoperative severity of illness depicted by the APACHE II score, SOFA score, and the American Society of Anesthesiologists (ASA) risk stratification are shown in Table 1.

All patients had evidence of systemic inflammatory response syndrome (SIRS).[18] The indicators of SIRS viz. respiratory rate, total leucocytic count, and temperature were statistically similar between both groups while heart rate was significantly higher in group H as compared to group L [Table 1]. The preoperative mean arterial pressure was also statistically similar between both groups [Table 1].

The presenting complaint in all patients was pain in abdomen or fever, with distribution of both symptoms being statistically similar in the groups [Table 2]. The mean duration of presenting complaint at the time of surgery, distribution of patients according to anatomical site of perforation, and the duration

Table 1: Preoperative patient characteristics

Parameter	Group H (n=42)	Group L (n=42)
Age (years)	35.9±13.5	36±11.8
IBW (kg)	57.1±6.8	59.7±7.0
Gender (M:F)	33:9	39:3
APACHE II score	5 [3-8]	5.5 [4-9]
SOFA score	2 [1-3]	2 [1-3]
ASA grade III	42 (100)	42 (100)
Respiratory rate (breaths/min)	30±7	31±5
Total leucocytic count (/mm^3)	7,400 [4,800-9,300]	8,600 [5,450-11,650]
Temperature (°C)	37.2±0.4	37.3±0.7
Heart rate (bpm)	119±14	110±16
Mean arterial pressure (mmHg)	83±10	86±8

Values are mean±SD or number of patients (%) or median interquartile range (IQR). Group H: High tidal volume ventilation (10 $ml.kg^{-1}$ IBW); group L: Low tidal volume ventilation (6 $ml.kg^{-1}$ IBW with PEEP of 10 cm H_2O); IBW=Ideal body weight

of surgery as well as intraoperative mechanical ventilation were also statistically similar in the two groups [Table 2].

The severity of peritonitis graded by the MPI score, the nature of peritonitis, type of peritoneal exudates, need of intraoperative dopamine infusion, and the maximum FiO_2 were statistically similar in the groups [Table 2].

The aggregate SOFA score; and that on first postoperative day were higher in group L as compared to group H [Table 3]. The maximum SOFA score was similar in the two groups [Table 3]. The all cause in-hospital mortality and incidence of re-exploration were similar in the two groups [Table 3]. The duration of hospital stay among survivors was statistically similar in the two groups [Table 3].

The values for all mediators i.e., IL-6, TNF-α, procalcitonin, and CRP were statistically similar in the two groups at all observed time intervals [Table 4 and Figures 1, 2].

Tidal volume was significantly lower for group L as compared to group H. Intraoperative respiratory rate was significantly higher, but minute ventilation was lower for group L as compared to group H [Table 5]. The P_{mean} was significantly higher for group L as compared to group H at all time points. P_{peak} was also significantly higher for group L at all time points [Table 5].

Discussion

Low tidal volume ventilation strategy resulted in significantly worse organ dysfunction indicated by higher aggregate

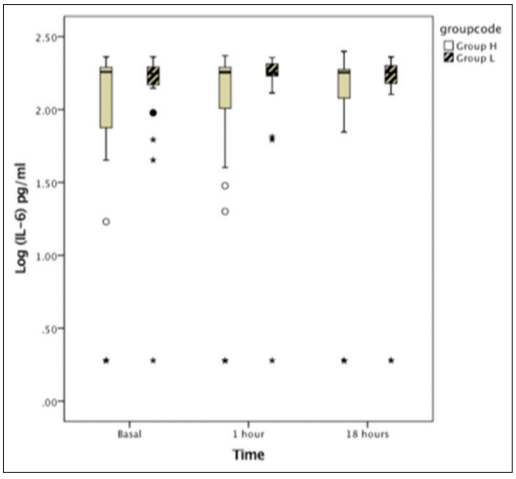

Figure 1: Interleukin-6 values were statistically similar between the two groups at observed time points i.e., prior to (basal), 1 h after the initiation of mechanical ventilation, and at 18 h postoperatively

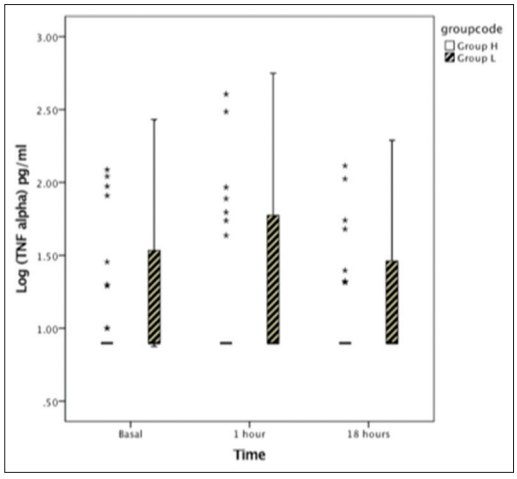

Figure 2: Tumor necrosis factor-α values were statistically similar between the two groups at observed time points i.e., prior to (basal) and 1 h after the initiation of mechanical ventilation, and at 18 h postoperatively

Table 2: Intraoperative and surgical characteristics

Characteristic	Group H (*n*=42)	Group L (*n*=42)	*P*
Presenting complaints			
Pain abdomen	40 (95)	42 (100)	0.494
Fever	14 (33)	14 (33)	1.000
Duration of presenting complaints (days)	2 [1-4]	3 [2-4]	0.454
Site of perforation			0.474
Ileum	24 (57)	24 (57)	
Jejunum	1 (2)	2 (5)	
Duodenum	9 (21)	13 (31)	
Appendix	4 (9)	2 (5)	
Large intestine	4 (9)	1 (2%)	
Duration of surgery (h)	1.5±0.5	1.7±0.7	0.127
Duration of mechanical ventilation (h)	1.8±0.5	2.1±0.7	0.084
MPI score	22 [14-27]	20 [14-28]	0.676
Nature of peritonitis (diffuse: localized)	40:2	42:0	0.494
Nature of exudates (clear:faeculant:purulent)	17:15:10	21:16:5	0.346
Use of dopamine (yes)	2	2	0.803
Maximum FiO_2 used	0.48±0.06	0.50±0.17	0.147

Values are mean±SD or median interquartile range (IQR) or number of patients (%). Group H: High tidal volume ventilation (10 ml.kg^{-1} ideal body weight); group L: Low tidal volume ventilation (6 ml.kg^{-1} ideal body weight with PEEP of 10 cmH2O); MPI=Mannheim Peritonitis Index

SOFA score as well as the score on first postoperative day. There was, however, no significant difference in the systemic inflammatory mediators that were measured upto 18 h postoperatively.

We included patients of perforation peritonitis with clinical evidence of SIRS and undergoing emergency laparotomy. Herein, the diagnosis of SIRS was based on derangement of any two out of four variables including heart rate, respiratory rate, temperature, or total leucocytic count.[18] The median preoperative levels of IL-6, TNF-α, procalcitonin, as well as CRP suggest presence of systemic inflammatory response. Procalcitonin >2 ng.ml^{-1} is strongly indicative of bacterial sepsis and CRP >50–100 ng.l^{-1} depicts moderate severity of sepsis.[19] We observed much higher levels of both inflammatory mediators, with basal procalcitonin levels of 8.5 [7.7–8.6] and 5.0 [5.6–8.7] ng.ml^{-1} for the groups receiving high and low tidal volume ventilation, respectively; and CRP levels approximating 175 ng.ml^{-1} in both groups. Plasma IL-6 levels of 38.7 pg.ml^{-1} have been reported to corroborate with infection[20] and the median levels were much higher in our patients (approximating 180 pg.ml^{-1}).

Effect of intraoperative ventilation employing low tidal volume on postoperative organ functions in patients with pre-existing systemic inflammatory response/sepsis has not been evaluated previously. There are studies, however, that have evaluated its role in affecting clinical outcomes including respiratory mechanics in patients without evidence of systemic inflammation.[21-27] Herein, low tidal volume strategy was associated with benefits like significant decrease in postoperative pulmonary and extrapulmonary complications following abdominal surgeries,[24] and need of postoperative

Table 3: Postoperative clinical course

Parameter	Group H (*n*=42)	Group L (*n*=42)	*P*
Aggregate SOFA score	1 [1-3]	3 [1-3]	0.048
Maximum SOFA score	1 [0-3]	2 [1-3]	0.055
SOFA score (POD1)	1 [0-3]	2 [1-3]	0.021
SOFA score (POD2)	1 [0-2]	1 [0-2]	0.471
SOFA score (POD3)	0 [0-1]	0 [0-1]	0.540
In-hospital mortality	2	4	0.676
Re-exploration laparotomy	0	1	0.494
Hospital stay* (days)	7 [5-10]	7 [5-8]	0.437

*Values are median interquartile range (IQR) or number of patients. Group H: High tidal volume ventilation (10 ml/kg^{-1} ideal body weight); group L: Low tidal volume ventilation (6 ml/kg^{-1} ideal body weight with PEEP of 10 cm H_2O); SOFA score: Sepsis-related Organ Failure Assessment score; POD: Postoperative day; *Amongst survivors only*

Table 4: Cytokine measurements

	Group H	Group L	*P*
TNF-α (basal) (pg.ml^{-1})	7.9 [7.9-7.9]	7.9 [7.9-34.9]	0.062
TNF-α (1 h) (pg.ml^{-1})	7.9 [7.9-7.9]	7.9 [7.9-70.7]	
TNF-α (18 h) (pg.ml^{-1})	7.9 [7.9-7.9]	7.9 [7.9-28.9]	
IL-6 (basal) (pg.ml^{-1})	181 [73.2-195]	176.3 [147.2-196.2]	0.105
IL-6 (1 h) (pg.ml^{-1})	180 [86.5-195]	178 [167.5-206.1]	
IL-6 (18 h) (pg.ml^{-1})	179.5 [117.3-188]	179 [149-201]	
Procalcitonin (basal) (ng.ml^{-1})	8.5 [7.7-8.6]	5.0 [5.6-8.7]	0.136
Procalcitonin (1 h) (ng.ml^{-1})	8.6 [6.0-8.8]	8.2 [3.6-8.8]	
Procalcitonin (18 h) (ng.ml^{-1})	8.7 [8.1-8.8]	8.6 [6.0-8.7]	
CRP (basal) (mg.l^{-1})	177.5 [172.4183.9]	175.8 [171.2-176.5]	0.556
CRP (1 h) (mg.l^{-1})	178.6 [172.7-179.9]	176.9 [175.3-179.4]	
CRP (18 h) (mg.l^{-1})	177.7 [171.8-181.0]	176.5 [174.6-181.4]	

Group H: High tidal volume ventilation (10 ml/kg^{-1} ideal body weight); group L: Low tidal volume ventilation (6 ml/kg^{-1} ideal body weight with PEEP of 10 cm H_2O). P of repeated measure ANOVA for comparison between the groups

Table 5: Intraoperative ventilatory parameters

Time point	Respiratory rate (/min)		Minute ventilation (l/min)		P_{mean} (cm H_2O)		P_{peak} (cm H_2O)	
	Group H (*n*=42)	Group L (*n*=42)	Group H (*n*=42)	Group L (*n*=42)	Group H (*n*=42)	Group L (*n*=42)	Group H (*n*=42)	Group L (*n*=42)
Baseline†	10±0	10±1	5.7±1.4	4.5±0.9*	8.5±3.4	13.1±1.4*	21.7±5.6	22.8±3.1
15 min††	10±0	12±2*	5.8±1.4	4.9±1.1*	8.4±3.2	13.2±1.2*	20.6±4.1	23.0±2.7*
30 min††	10±1	13±2*	5.7±1.5	5.0±1.1*	8.5±2.9	13.1±1.4*	20.7±3.5	23.1±2.7*
45 min††	10±1	13±2*	5.8±1.2	5.1±1.2*	8.1±2.7	13.4±1.5*	20.4±3.4	23.1±2.9*
60 min††	10±1	13±2*	5.9±1.3	5.0±1.2*	8.5±2.8	13.3±1.3*	20.6±3.3	23.0±2.4*
75 min††	10±1	13±2*	6.0±1.3	5.0±1.2*	8.5±2.8	13.5±1.4*	20.6±4.1	23.0±2.6

*Values are mean±SD. Group H: High tidal volume ventilation (10 ml/kg^{-1} ideal body weight); group L: Low tidal volume ventilation (6 ml/kg^{-1} ideal body weight with PEEP of 10 cm H_2O); $ETCO_2$: End tidal carbon dioxide; †After initiation of mechanical ventilation; ††Depict the designated time elapsed following recording of baseline value; *P<0.05 for group H versus group L at respective time point*

ventilation.[28] A decrease in postoperative organ failure and ICU stay were also observed following cardiac surgery.[25]

However, the effects of intraoperative short-term ventilation strategy, including on the biotrauma and consequently on organ functions may differ in patients with pre-existing systemic inflammation/sepsis.

Also, earlier publications appear to focus primarily on respiratory function or outcomes.[23-27] We hypothesized that biotrauma-induced inflammatory response should have a multi-organ effect and not be confined only to the respiratory system. Thus, we observed the effect on composite organ functions indicated by SOFA score.

There was significantly worse organ function with low tidal volume ventilation, suggesting a deterioration of the inflammatory response/sepsis. Although we could not locate any trial evaluating effects of low tidal volumes in patients with systemic inflammation/sepsis, Futier *et al*. had observed a significant decrease in postoperative sepsis following use of short-term low tidal volume ventilation.[24] This is contrasting to the worse outcome with low tidal volume ventilation seen in our study. Not all previous results have found benefits with low tidal volume ventilation. In a recent study by Bates *et al*., use of low tidal volumes in patients undergoing pulmonary thromboendarterectomy failed to improve the clinical outcome, similar to some earlier trials.[5,26,29] Also, lowered volumes have been noted to produce a worse inflammatory response,[30,31] or lack of any significant improvement in inflammatory mediators.[5,15,21,22] Thus, it could be possible that ventilation-induced inflammatory responses are worsened by low tidal volume ventilation strategy in patients with pre-existing systemic inflammation.

The worse organ functions with low tidal volume ventilation were not supported by a corroborating increase in the inflammatory mediators in our study. Various inflammatory mediators have been measured to evaluate biotrauma. The commonly used markers include IL-6 and TNF-α with the former also relating to clinical outcome following ventilation.[2,4-6,9,21,22] We included procalcitonin and CRP level evaluation in addition, albeit in a small subset, since both are known to be markers of severity of sepsis.[19] The levels of all inflammatory mediators were statistically similar between both ventilation strategies at all times. However, procalcitonin was insignificantly greater at 1 h after initiation of ventilation with lowered tidal volume. Our study was not powered to detect significant differences in the systemic markers of inflammation that were included as a secondary objective. Also, the time course for evaluation of the SOFA score and inflammatory markers was different. While the aggregate SOFA score represented the entire hospital stay, inflammatory markers were measured only upto 18 h postoperatively. Both these reasons may explain the contrasting result of significantly worse organ functions without any apparent difference in inflammatory mediators with low versus high tidal volume ventilation. Also, all clinical interventions have a potential to alter patient outcome including organ functions. While the aim of our study was not to protocolize the clinical management in terms of sepsis bundles etc., the perioperative management was as per routine clinical practice and similar in both groups, and hence unlikely to have affected the SOFA score differently between both groups. Further research with longer evaluation periods for the inflammatory mediators and powered to detect significant differences is required to arrive at a conclusion.

Patients of intestinal perforation peritonitis with SIRS were recruited for this study. We included patients of perforation peritonitis to represent pre-existing systemic inflammatory response. Intestinal perforation leads to contamination of peritoneal cavity with microbial flora thereby triggering a local inflammatory response.[32] Following this, a systemic expression of inflammatory response ensues which leads to sepsis if not contained by host mechanisms.[32]

In most previous studies comparing low with high tidal volume strategy, PEEP ranging from 5 to 10 cmH_2O is used with the former. A PEEP of 10 cmH_2O minimizes tidal recruitment and de-recruitment during anesthesia while lower levels of PEEP may paradoxically increase regional shear stress and lung injury.[33] Thus we used PEEP of 10 cmH_2O with the lowered tidal volume of 6 $ml.kg^{-1}$.

We used dopamine in our study because at the time of conceptualization of this trial, dopamine was the recommended inotrope of choice as per the SSC guidelines.[34] They were later modified to include noradrenaline as drug of choice.[35]

The demographic and epidemiologic profile of patients in both groups is in unison with previously documented data from the Indian subcontinent regarding patients of perforation peritonitis. There was a predominance of young male patients, pain in abdomen was a common presenting compliant, and the commonest site of intestinal perforation was the ileum.[12]

For comparison between both groups, preoperative severity of illness was quantified using the APACHE II, MPI, and SOFA scores. All of the three scores were statistically similar between both groups. APACHE II has been used successfully to quantify severity of illness in patients of perforation peritonitis. While APACHE II score uses several physiologic parameters to quantify severity of an illness, the MPI score is specifically designed for severity assessment of perforation peritonitis and is frequently used

in these patients.[16,36] Besides taking into account the presence of age, gender, organ failure, and presence of malignancy, it includes the duration of peritonitis and extent as well as character of peritoneal fluid. We used the MPI score in addition to APACHE II keeping in view the additional consideration given to nature of peritonitis in this score. Patients with perforation peritonitis are known to suffer the sequelae of sepsis including organ dysfunction, and SOFA is one of the commonest scores to assess organ dysfunction/failure in patients of sepsis.

Based on our observations we conclude that use of low tidal volume of 6 $ml.kg^{-1}$ along with PEEP of 10 cmH_2O is associated with significantly worse postoperative organ functions as compared to volume of 10 ml kg^{-1} without PEEP in patients of perforation peritonitis-induced systemic inflammation undergoing emergency laparotomy. We believe our observations could be of value in adding to existing role of low tidal volume ventilation (with PEEP) in surgical patients with pre-existing inflammatory response/sepsis.

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Conflicts of interest

There are no conflicts of interest.

Trial registered with the Clinical Trial Registry of India.

(Registration number CTRI/2015/12/006403 dated 2.12.15).

References

1. Stapleton RD, Steinberg KP. Ventilator induced lung injury. In: MacIntyre NR, Branson RD, editors. Mechanical Ventilation. Missouri: Elsevier; 2009. p. 206-15.
2. Acute Respiratory Distress Syndrome Network. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A, *et al.* Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
3. Choi G, Wolthuis EK, Bresser P, Levi M, Van der Poll T, Dzoljic M, *et al.* Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents alveolar coagulation in patients without lung injury. Anesthesiology 2006;105:689-95.
4. Michelet P, D'Journo XB, Roch A, Doddoli C, Marin V, Papazian L, *et al.* Protective ventilation influences systemic inflammation after esophagectomy: A randomized controlled study. Anesthesiology 2006;105:911-9.
5. Wolthuis EK, Choi G, Dessing MC, Bresser P, Lutter R, Dzoljic M, *et al.* Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents pulmonary inflammation in patients without preexisting lung injury. Anesthesiology 2008;108:46-54.
6. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, *et al.* Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: A randomized controlled trial. JAMA 1999;282:54-61.
7. Zhang H, Downey GP, Suter PM, Slutsky AS, Ranieri VM. Conventional mechanical ventilation is associated with bronchoalveolar lavage-induced activation of polymorphonuclear leukocytes: A possible mechanism to explain the systemic consequences of ventilator-induced lung injury in patients with ARDS. Anesthesiology 2002;97:1426-33.
8. Pinheiro de Oliveira R, Hetzel MP, dos Anjos Silva M, Dallegrave D, Friedman G. Mechanical ventilation with high tidal volume induces inflammation in patients without lung disease. Crit Care [online serial] 2010;14:R39.
9. Zupancich E, Paparella D, Turani F, Munch C, Rossi A, Massaccesi S, *et al.* Mechanical ventilation affects inflammatory mediators in patients undergoing cardiopulmonary bypass for cardiac surgery: A randomized clinical trial. J Thorac Cardiovasc Surg 2005;130:378-83.
10. Slutsky AS, Tremblay LN. Multiple system organ failure: Is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 1998;157:1721-5.
11. Dreyfuss D, Saumon G. From ventilator-induced lung injury to multiple organ dysfunction? Intensive Care Med 1998;24:102-4.
12. Jhobta RS, Attri AK, Kaushik R, Sharma R, Jhobta A. Spectrum of perforation peritonitis in India--review of 504 consecutive cases. World J Emerg Surg 2006;1:26.
13. Ceriani R, Mazzoni M, Bortone F, Gandini S, Solinas C, Susini G, *et al.* Application of the sequential organ failure assessment score to cardiac surgical patients. Chest 2003;123:1229-39.
14. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, *et al.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707-10.
15. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med 1985;13:818-29.
16. Billing A, Fröhlich D, Schildberg FW. Prediction of outcome using the Mannheim peritonitis index in 2003 patients. Peritonitis Study Group. Br J Surg 1994;81:209-13.
17. Tyagi A, Bansal A, Das S, Sethi AK, Kakkar A. Effect of thoracic epidural block on infection-induced inflammatory response: A randomized controlled trial. J Crit Care 2017;38:6-12.
18. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, *et al.* Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644-55.
19. Meisner M. Update on procalcitonin measurements. Ann Lab Med 2014;34:263-73.
20. Kellum JA, Kong L, Fink MP, Weissfeld LA, Yealy DM, Pinsky MR, *et al.*; GenIMS Investigators. Understanding the inflammatory cytokine response in pneumonia and sepsis: Results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. Arch Intern Med 2007;167:1655-63.
21. Memtsoudis SG, Bombardieri AM, Ma Y, Girardi FP. The effect of low versus high tidal volume ventilation on inflammatory markers in healthy individuals undergoing posterior spine fusion in the prone position: A randomized controlled trial. J Clin Anesth 2012;24:263-9.
22. Wrigge H, Uhlig U, Zinserling J, Behrends-Callsen E, Ottersbach G, Fischer M. The effects of different ventilatory settings on pulmonary

and systemic inflammatory responses during major surgery. Anesth Analg 2004;98:775-81.
23. Sundar S, Novack V, Jervis K, Bender SP, Lerner A, Panzica P, *et al.* Influence of low tidal volume ventilation on time to extubation in cardiac surgical patients. Anesthesiology 2011;114:1102-10.
24. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, *et al.* IMPROVE Study Group. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med 2013;369:428-37.
25. Lellouche F, Dionne S, Simard S, Bussières J, Dagenais F. High tidal volumes in mechanically ventilated patients increase organ dysfunction after cardiac surgery. Anesthesiology 2012;116:1072-82.
26. Weingarten TN, Whalen FX, Warner DO, Gajic O, Schears GJ, Snyder MR, *et al.* Comparison of two ventilatory strategies in elderly patients undergoing major abdominal surgery. Br J Anaesth 2010;104:16-22.
27. Treschan TA, Kaisers W, Schaefer MS, Bastin B, Schmalz U, Wania V, *et al.* Ventilation with low tidal volumes during upper abdominal surgery does not improve postoperative lung function. Br J Anaesth 2012;109:263-71.
28. Guay J, Ochroch EA. Intraoperative use of low volume ventilation to decrease postoperative mortality, mechanical ventilation, lengths of stay and lung injury in patients without acute lung injury. Cochrane Database Syst Rev 2015;12:CD011151.
29. Bates DM, Fernandes TM, Duwe BV, King BO, Banks DA, Test VJ, *et al.* Efficacy of a low-tidal volume ventilation strategy to prevent reperfusion lung injury after pulmonary thromboendarterectomy. Ann Am Thorac Soc 2015;12:1520-7.
30. Sato H, Nakamura K, Baba Y, Terada S, Goto T, Kurahashi K. Low tidal volume ventilation with low PEEP during surgery may induce lung inflammation. BMC Anesthesiol 2016;16:47.
31. Vaneker M, Joosten LA, Heunks LM, Snijdelaar DG, Halbertsma FJ, van Egmond J, *et al.* Low-tidal-volume mechanical ventilation induces a toll-like receptor 4-dependent inflammatory response in healthy mice. Anesthesiology 2008;109:465-72.
32. Sido B, Teklote JR, Hartel M, Friess H, Büchler MW. Inflammatory response after abdominal surgery. Best Pract Res Clin Anaesthesiol 2004;18:439-54.
33. Neumann P, Rothen HU, Berglund JE, Valtysson J, Magnusson A, Hedenstierna G. Positive end-expiratory pressure prevents atelectasis during general anaesthesia even in the presence of a high inspired oxygen concentration. Acta Anaesthesiol Scand 1999;43:295-301.
34. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, *et al.* Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296-327.
35. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, *et al.* Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.
36. Torer N, Yorganci K, Elker D, Sayek I. Prognostic factors of the mortality of postoperative intraabdominal infections. Infection 2010;38:255-60.